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## **Autophagy in cellular transformation, survival and communication with the tumor microenvironment**

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**Abstract:** Autophagy describes several metabolic pathways, by which cytoplasmic constituents are imported into lysosomes for degradation. These pathways and in particular macroautophagy play an important role during oncogenesis by apparently inhibiting cellular transformation initially, but then ensuring tumor cell survival in established cancers. Furthermore, the conditioning of the tumor microenvironment, including the cross-talk with the immune system, is influenced by autophagy. These multiple facets of autophagy regulation in tumors will be discussed in the series of review articles of this issue of Seminars in Cancer Biology. A comprehensive understanding of this pathway in oncology is needed to efficiently apply autophagy regulating tumor therapies, which are already in use.

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## Editorial

**Autophagy in cellular transformation, survival and communication with the tumor microenvironment****Abstract**

Autophagy describes several metabolic pathways, by which cytoplasmic constituents are imported into lysosomes for degradation. These pathways and in particular macroautophagy play an important role during oncogenesis by apparently inhibiting cellular transformation initially, but then ensuring tumor cell survival in established cancers. Furthermore, the conditioning of the tumor microenvironment, including the cross-talk with the immune system, is influenced by autophagy. These multiple facets of autophagy regulation in tumors will be discussed in the series of review articles of this issue of *Seminars in Cancer Biology*. A comprehensive understanding of this pathway in oncology is needed to efficiently apply autophagy regulating tumor therapies, which are already in use.

Autophagy comprises at least three metabolic pathways that deliver cytoplasmic constituents for lysosomal degradation [1, 2]. During microautophagy substrates invaginate either into the lysosomal or late endosomal membrane for degradation by lysosomal hydrolases. Chaperone-mediated autophagy translocates proteins in a signal peptide dependent manner across the lysosomal membrane. Finally, macroautophagy engulfs cytoplasmic content, including damaged organelles, protein aggregates and cytosolic pathogens, with a double-membrane, which upon closure forms an autophagosome that then fuses with lysosomes or late endosomes. Macroautophagy is the most intensively studied mechanisms of the three pathways and its role for cancer biology will be primarily discussed in the reviews of this issue of *Seminars in Cancer Biology*.

Macroautophagy requires more than 30 autophagy-related proteins to initiate autophagosome formation at a membrane, to complete autophagosome formation around its cargo, and to regulate fusion of autophagosomes with other membrane compartments. Three reviews will address these molecular mechanisms for macroautophagy in cancer cells. Sharon Tooze and colleagues will discuss the regulation of the ULK1/Atg1 and Beclin1/Atg6-PI3KC3 complexes in autophagosome initiation [3]. These two complexes are essential for macroautophagy and targeted in tumor cells to manipulate the pathway. Furthermore, Guido Kroemer and coworkers will out-line the influence of stress-induced transcription factors on macroautophagy in cancer cells [4]. This regulation of macroautophagy is especially important during up-regulation of macroautophagy in established tumors. Finally, Michael Overholtzer and his co-author will focus on an alternative use of the molecular core machinery of macroautophagy in regulating phagocytosis [5]. This alternative use of macroautophagy components has to be kept in mind, when analyzing this pathway and exploring its therapeutic regulation.

A second set of reviews will explore the dichotomy of macroautophagy regulation in tumors. Curiously, a picture has emerged in recent years that macroautophagy blocks

transformation initially, and therefore genetic loss of macroautophagy components can be observed in some tumors, while the nutrient starvation conditions in established tumors, require then epigenetic macroautophagy up-regulation for the survival of the tumor. Along these lines, Mauro Piacentini and colleagues will discuss such genetic alterations of macroautophagy and their epigenetic compensation in melanoma as a tumor example [6]. Kevin Ryan and co-worker will out-line, how these macroautophagy regulations intersects with cell death [7]. Finally, Hans-Uwe Simon and his co-authors will explore, how tumor therapies already manipulate macroautophagy [8]. These reviews focus on the cell intrinsic requirements of tumor cells to regulate macroautophagy during tumor growth.

The final set of reviews then characterizes, how the very same modulations of macroautophagy also influence the communication of tumor cells with their microenvironment. Patrice Codogno and colleagues out-line how the changes in nutritional requirements during tumorigenesis can also be overcome by inducing macroautophagy in the tumor microenvironment [9]. In this discussion, genetic lesions that down-regulate macroautophagy initially for transformation are juxtaposed to mechanisms that up-regulate nutrient production via macroautophagy up-regulation in accessory cells in tumors. Michael Lotze and coworkers then describe how macroautophagy in tumor cells influences the inflammatory environment of the tumor (Lotze et al., *Semin Cancer Biol* 2013). These mechanisms allow immune activation and visualization of tumors to the immune system. We complete this set of reviews by discussing, how macroautophagy then influences the presentation of tumor antigens for tumor rejection or tolerance induction [10]. In this respect the catabolic products of this pathway are reused by the immune system to monitor the health of the tumor cell proteome. Thus, macroautophagy does not only regulate the metabolism of tumor cells directly, but also via manipulating the cancer microenvironment.

These many facets of the role of macroautophagy in cancer biology make it an attractive, but also complicated pathway to manipulate for the benefit of patients. In part the timing of

therapeutic intervention by macroautophagy regulation will be decisive for the outcome. Nevertheless, with new reagents that can therapeutically regulate macroautophagy [11, 12] for clinical benefit in infectious diseases, neurodegeneration and tumors [13], more specific and finely tuned interventions can be performed. The knowledge on the regulation of macroautophagy during tumorigenesis that has been gathered during the last years, will guide these therapeutic approaches.

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